with adenosine is insufficient, and will underestimate the hemodynamic significance of most bridges. Likewise, myocardial bridges cause significant diastolic pressure gradients, but normal or negative systolic pressure gradients (systolic distal pressure, Pd is greater than systolic proximal pressure, Pa) as a result of systolic pressure overshooting. This produces an artificial elevation in the mean pressure used by traditional FFR, again resulting in an underestimation of hemodynamic significance. Therefore, diastolic FFR with dobutamine challenge is currently the technique of choice in testing for hemodynamically significant myocardial bridging. Of note, the tracings used by the authors to demonstrate hemodynamics in myocardial bridging (Figure 7 in the paper by Corban et al.) (1), are actually not consistent with expected pressure tracings because the Pd is reduced compared with the Pa. This suggests either an element of coronary spasm or fixed stenosis, rather than a significant myocardial bridge.

Second, as a novel noninvasive diagnostic technique, stress echocardiography has been shown to identify myocardial bridges (3). Specifically, one sees a unique wall motion abnormality of mid septal buckling during peak stress, which distinguishes itself from a fixed left anterior descending (LAD) artery stenosis by not involving the apex. We have demonstrated that this finding of focal septal buckling with apical sparing mirrors the hemodynamics seen within and distal to the bridge. The most significant increases in flow velocity and decreases in diastolic pressure are almost invariably located within the myocardial bridge, not distal to it as is traditionally thought. We have postulated a Venturi-like effect within the bridge, resulting in local (mid septal) ischemia rather than distal ischemia.

Third, there is an ongoing misconception about the location of plaque in relation to the myocardial bridge. The maximal plaque burden is not at the entrance of the bridge, but on average 20 mm to 30 mm proximal to the entrance of the bridge (3,4). This may be attributable to the reversal of systolic flow seen on Doppler tracings, in which retrograde flow collides with antegrade flow, causing high *systolic* wall shear stress (WSS) upstream from the bridge entrance. The high systolic WSS referred to in Figure 1 in the paper by Corban et al. (1) is actually caused by external wall compression, not affecting WSS inside the bridge. During *diastole*, the WSS is low proximal and distal to the bridge, and even lower within the bridge. Recognition of the location of maximal plaque burden is important because it has been shown that stents placed proximal to or extending into bridges have higher rates of target lesion revascularization.

Finally, it should be clarified that the "half-moon" sign seen on intravascular ultrasound (IVUS) directly corresponds to muscle tissue (5), not adipose tissue, perivascular fat, or adventitia, as has been previously suggested.

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REPLY: Myocardial Bridging

We appreciate the interest generated by our review paper on myocardial bridging (1). In response to comments by Dr. Tremmel and colleagues, we have attempted to describe the complex pathophysiology of myocardial bridging with emphasis on both systolic and diastolic flow abnormalities that can coexist with atherosclerotic plaque proximal to the bridge, negative remodeling within the bridged segment, or coronary vasospasm. We believe that it is reasonable to begin the physiologic evaluation with fractional flow reserve (FFR) with adenosine administration measured distal to a myocardial bridge. If abnormal, this indicates concomitant fixed obstruction from either plaque proximal to the bridge, negative remodeling within the bridge, or coronary vasospasm. It is true that mean FFR measured within the bridge may underestimate the maximal gradient as

the distal pressure gets ventricularized with systolic overshoot to the point of developing a negative systolic gradient. This phenomenon can also be observed distal to the bridge, and diastolic FFR may unmask larger gradients. The dobutamine challenge is performed to interrogate the dynamic contribution of increased contractility and tachycardia on the pressure gradient. As with adenosine, dobutamine gradients in diastole may exceed those in systole because of myocardial compression. The elegant paper by Escaned et al. (2) demonstrated that combining low-dose intracoronary adenosine (20 μg) with moderate-dose intravenous dobutamine infusion (20 μg/kg/min) increased the likelihood of unmasking larger diastolic pressure gradients (5 of 12 patients). Lin et al. (3) reported that diastolic FFR correlated with septal buckling on exercise echocardiography in 14 patients. Another study of 18 patients with myocardial bridging reported that dobutamine challenge was successfully performed in 13 of 18 patients. Dobutamine-induced diastolic FFR did result in larger gradients in 3 patients; however, it was not a predictor of major adverse cardiac events (4). Taken together, it is clear that there are limited data correlating diastolic FFR with adenosine, dobutamine, or combined adenosine and dobutamine with noninvasive parameters of ischemia or clinical outcomes. In our practice, when adenosine- and dobutamine-induced FFR are negative, we test for coronary vasospasm using intracoronary acetylcholine (off-label use) as the demonstration of vasospasm without a significant bridge might be a scenario in which nitrate therapy can be considered.

With regard to comments about wall shear stress (WSS), any reversal of systolic flow proximal to the bridge that collides with antegrade flow would not lead to an increase in WSS. The momentum, which is a vector quantity, of these opposing flow fields would result in a decrease in fluid velocity at this location and lower WSS values as we point out. Furthermore, it should be noted that the higher pressure values that have been measured proximal to a bridge would lead to higher wall stress within the arterial tissue (solid mechanics), assuming constant material properties, and not WSS, a fluid induced mechanical stress. Our computational fluid dynamics simulations (5) assume a rigid wall (i.e., no external myo-cardial compression is included). Thus, the high WSS values within the bridge observed in our figure are solely a result of the lumen anatomy, both arterial radius and curvature. Anatomy aside, the high WSS values within the bridge should be expected on the basis of clinical data. As has been reported (2), abnormal FFR values within the myocardial bridge indicate that intrabridge velocity values are higher (Bernoulli's principle), which would result in high WSS values as compared with the proximal and distal regions.

We agree with Dr. Angelini that a thorough workup to exclude concomitant atherosclerosis or vasospasm can be valuable for patients with symptoms refractory to medical therapy and that detailed physiologic evaluation should be limited to centers with experience in the field. As he indicates, although the intravascular ultrasound (IVUS) "half-moon" sign is a characteristic finding of myocardial bridges, the etiology of the sign remains controversial. A recently published autopsy image suggests that the echolucent finding on IVUS might reflect a muscle band, although the autopsy IVUS image in the paper may not be characteristic of a clinically observed half-moon sign. We also agree with Dr. Angelini that symptoms of chest pain, myocardial infarction, and sudden death are uncommon relative to the prevalence of myocardial bridging and that correlating symptoms with data from diagnostic testing to identify whether or not symptoms are related to myocardial bridging, concomitant vasospasm, atherosclerosis, or none of the preceding is often challenging. Large prospective registries are warranted to better define the role of myocardial bridging in symptoms, flow disturbances, endothelial dysfunction, atherosclerosis development, and prognosis of these patients.

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MicroRNA-29, a Mysterious Regulator in Myocardial Fibrosis and Circulating miR-29a as a Biomarker

Myocardial fibrosis is characterized by pathological modification of myocardium, in which cardiomyocytes undergo apoptosis and the heart tissue is replaced by fibroblasts; this phenomenon is usually referred to as cardiac remodeling. However, the pathogenesis of myocardial fibrosis is still unclear despite advances in our understanding of the ischemic process.

MicroRNAs (miRs), small endogenous noncoding RNAs, have a well-documented role in the regulation of the cardiovascular system. miRs such as miR-29 and miR-21 have been shown to have a role in the genesis of myocardial fibrosis.

Roncarati et al. (1) measured a set of miRs in the plasma of patients with hypertrophic cardiomyopathy to understand which miRs can be regarded as biomarkers of this disease. Only miR-29a levels were found to correlate with cardiac fibrosis, along with several miRs related to cardiac hypertrophy. This discovery is significant in that it may help define patients who may develop fibrosis. However, it is important to know where miR-29a comes from and what types of cells, cardiomyocytes or fibroblasts, secrete it. Previous studies have shown the opposite effect of miR-29 in different types of cells (2–5). On one hand, miR-29 can promote cardiomyocyte apoptosis via down-regulation of antiapoptosis genes, such as Bcl-2, CDC42, and Tcl-1 (2–4); on the other hand, miR-29 can protect against fibrosis through inhibition of collagens released from extracellular matrix (5). Because the majority of cell types change from cardiomyocyte to myofibroblast phenotype during progression of cardiac remodeling, it is reasonable to hypothesize that up-regulation of miR-29a in the plasma of these patients is mainly due to cardiomyocyte apoptosis and not secretion from fibroblasts. It is also possible that the up-regulation of miR-29a in plasma reflects the body's attempt to express more fibrosis-protective mediators to prevent adverse cardiac remodeling.

Cardiac remodeling is a complicated process that involves a number of molecular and pathological alterations (5). A simple measurement of miRs at one time point may not be enough to define molecular changes. Identification of miR-29a (and other miRs) in different cell types and at different time points is necessary before recognizing it as a biomarker for cardiac remodeling.

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REPLY: MicroRNA-29, a Mysterious Regulator in Myocardial Fibrosis and Circulating miR-29a as a Biomarker

We thank Dr. Dai and colleagues for their interest in our paper (1). As their letter suggests, it is possible that microRNA (miR)-29 is secreted by more than one cell type. However, our intention was not to address this question, which has been partly done and should be tackled further in other settings and with appropriate technologies (tissue-specific knockout mice, transgenic mice, and so on); we simply found a significant correlation between a few circulating miRs, in particular miR-29a, and the degree of cardiac fibrosis in patients with hypertrophic cardiomyopathy.

We therefore agree with the concept expressed in the letter by Dr. Dai and colleagues that miR-29s are expressed in many cell types, where it probably plays